IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MARISE S. GOTTLIEB *et al.*

Serial No.:	10/804,954	Examiner:	CORDERO GARCIA, MARCELA M
Filed:	19 March 2004	Art Unit:	1654

For: METHOD FOR TREATING CONDITIONS ASSOCIATED WITH THE METABOLIC SYNDROME

TRANSMITTAL OF DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This transmittal accompanies an executed Declarations Under 37 C.F.R §1.132 for the above-referenced application.

Respectfully submitted,

Robert E. Bushnell,
Attorney for the Applicant
Registration No.: 27,774

Suite 300, 1522 "K" Street, N.W.
Washington, D.C. 20005
(202) 408-9040

Folio: P56874
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I.D.: REB/ny

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DECLARATION OF DR. MARISE S. GOTTLIEB

1. I am Dr. Marise S. Gottlieb. The following statements are made on the basis of my personal observations of the facts stated and where any opinions are stated they reflect my actual beliefs.

2. I received my Baccalaureate degree in Chemistry from Barnard College of Columbia University, New York, in 1958 and my Doctor of Medicine Degree from New York University Medical School in 1962. I also trained in Epidemiology in the Department of Epidemiology, Harvard University School of Public Health (1965-68, M.P.H., 1966), am Board Certified in General Preventive Medicine (1971), and am a Fellow in the American College of General Preventive medicine and the American College of Epidemiology. I was Instructor in Medicine at Harvard Medical School, Boston, MA, Assistant Professor of Community Medicine, College of Medicine and Dentistry of New Jersey, Rutgers Medical School, Piscataway, NJ and Associate Professor of Medicine at Tulane University School of Medicine, and Associate Professor of Epidemiology at Tulane University School of Public Health and Tropical Medicine where I taught courses in Epidemiology.

I am recognized for my studies on the heredity of Diabetes Mellitus, having described the difference in the role of genetics between Type I and Type II Diabetes Mellitus, further establishing the differences between these conditions. I established and was Principal Investigator for a MRFIT (Multiple Risk Factor Interventional Trial for the Prevention of Coronary Heart Disease Clinical Center, sponsored by the National Institutes of Health) in New Jersey. In New Orleans, I conducted studies on Cancer in Louisiana supported by the National Cancer Institute and the Environmental Protection Agency and was a member of the Tumor Registry in Louisiana. I also designed, applied for, was awarded, and directed a Diabetes Control Demonstration Project at the Louisiana State Health Department, such Project being funded by the United States Centers for Disease Control and Prevention. I collaborated and published with Dr. A. Arthur Gottlieb in his studies on the clinical and biological effects of leukocyte-derived and synthetic immunomodulators on cell-mediated immune function, and on HIV and other diseases. I was involved in the design of the clinical testing of the immunomodulator technology and the analysis of the data which has been collected to date.

I am currently the President of Endeavor Corporation.

3. The Metabolic Syndrome is a complex constellation of symptoms and conditions which tend to appear in a cluster. That it is different than other conditions has been recognized by the world medical establishment and it has been assigned its own ICD Code (International Classification of Disease), 277.7, whereas the code for Diabetes Mellitus is 250 followed by a decimal point and number specifying the different "varieties" and status of the disease. Treatment of the Metabolic Syndrome is complex and depends on what parts of the constellation of conditions are present in any given individual. We need to be clear:

The Metabolic Syndrome is ***not equivalent to any type of Diabetes Mellitus or obesity***, although impaired glucose tolerance and obesity may well be components of the Metabolic Syndrome as it is expressed in a given individual. It must also be said that,

because there is variability in the expression of the Metabolic Syndrome, other than for inflammation, there is no universal treatment that has been found to treat it. Further, it must also be said that, although expert members of the medical establishment have tried, no clear treatment of the Syndrome has been found to be "obvious".

The instant application addresses an area of commonality which was discovered by extensive research into the various components of the Metabolic Syndrome and a sophisticated re-analysis of an experimental study in which immunomodulatory therapy indicated success.

It is critical that the examiner recognize that just because Rheumatoid Arthritis has an inflammatory component, it is not the same as the Metabolic Syndrome. Further, it is not valid to combine earlier A. Gottlieb patents with the instant application, as Dr. A. Gottlieb addressed the treatment of autoimmune diseases such as Rheumatoid Arthritis and Type I Diabetes Mellitus, which is clearly not the type of Diabetes found in the Metabolic Syndrome. (As well, Rheumatoid Arthritis and Type I Diabetes do not lead, as a result of the course of disease, to obesity.) Further, Dr. A. Gottlieb taught in his patents that the use of the technology described in the instant application affects autoimmune diseases as well as diseases involving immune deficiency. A careful search of Gottlieb's patents reveals that he did not teach in any way that the technology of the instant application would treat chronic inflammation. We point out again that the parenthetical list of autoimmune diseases in Dr. A. Gottlieb's patents that includes Rheumatoid Arthritis and Diabetes is a list of autoimmune diseases. The omission of Type I when referring to Diabetes in this list is a typographical error.

The examiner states that her search was broadened to include "impaired glucose tolerance associated with the Metabolic Syndrome." She then goes on to associate Diabetes and obesity with Gottlieb's teachings about Diabetes in prior patents, saying that impaired glucose tolerance is associated with Diabetes. There are numerous conditions and

reasons for impaired glucose tolerance, including Type I Diabetes which is the subject of Gottlieb's statements in prior patents. (Note that the term "Diabetes Mellitus", a term that dates to antiquity, simply refers to "sweet urine", a symptom of any number of conditions, some related only by that symptom.) The Examiner then states that giving of insulin can result in obesity and through some contorted logic, links all of the conditions and declares that what we claim (in the claims that she has not insisted be disallowed) is obvious or is present in other patents. She simply is not allowed, I believe, to make all of the "logical" jumps she makes, as they are not supported by the science. Further, the use of an immunomodulator to control a metabolic disease is certainly new, unique, and not obvious to anyone! Rather, it grew out of a sophisticated analysis of data collected and examined by Gottlieb and his colleagues. The Examiner is not allowed, I believe, to use hindsight, as she appears to be doing.

We stand by the arguments presented in our prior response. The examiner is equating Rheumatoid Arthritis with the glucose intolerance and/or Diabetes associated with the Metabolic Syndrome. She is not entitled to do so. If Rheumatoid Arthritis is an autoimmune disease, then it does, as we state, fall into a similar category of diseases as Type I Diabetes Mellitus. This is the relationship discussed by Dr. A. Gottlieb in the prior patents cited by the examiner.

Unfortunately, the Examiner has taken words from various sources and made assumptions of identity. Diabetes Mellitus can be Type I Diabetes Mellitus, Type II Diabetes Mellitus, or Diabetes Mellitus associated with the Metabolic Syndrome, all different conditions with different causes and different modes of treatment. To be specific:

Type I Diabetes Mellitus: an autoimmune disease which prevents production of insulin by cells of the pancreatic islets of Langerhans. It is a genetic disease with a recessive

pattern of inheritance (Gottlieb, M.S and Root, H.F. Diabetes Mellitus in Twins. *Journal of the American Diabetes Association*, 17:693-704 (1968).)
Type II Diabetes Mellitus is a genetic disorder with a dominant pattern of inheritance which involves failure of the end organ (for example, muscle and liver) to use insulin.

"Type II Diabetes Mellitus" associated with the Metabolic Syndrome is a general inflammatory response causing failure of the end organs to use insulin. This form of Diabetes Mellitus is not genetically inherited.

Next, the word obesity may be that associated with excess insulin or that associated with the metabolic syndrome, among other conditions, none of which are identical in cause or treatment. Taking words out of context to find reasons for rejection does not contribute to progress.

The instant application addresses a different set of relationships and disease indications. We do not deny that both the Diabetes included by Gottlieb and the Diabetes of the Metabolic Syndrome both result in elevated blood glucose. However the reason and the treatments are not the same. Further simply giving more insulin to a person with Metabolic Syndrome, as one might do to regulate the Diabetes included by Gottlieb, would not be expected by itself to reduce blood glucose, as the end-organs which require glucose would not be able to use that insulin.

Further, just because obesity may be associated with certain non-metabolic syndrome Diabetes therapy does not mean that it is caused by the same mechanism.

The equalities that the examiner is trying to draw simply are not valid. I believe that she is trying to use transitivity, i.e., if A is equal to B, and B is equal to C, then A is equal to C. However, obesity can have many root causes, as can elevated blood sugar, as can chronic irritation. To form equalities across all of these is incorrect. To do so would be

the same as to say that there is only one way to treat a person who is sneezing, where sneezing can be caused by a cold (viral) or, for example, by exposure to dust (a physical irritation), or by an allergic reaction. In the first case, there is no good treatment, in the second, one would put on a mask, and in the third, one would take an antihistamine. In no case would one treatment be expected to provide relief in place of the other.

In the same way, no one skilled in the art would presume that Diabetes listed with Rheumatoid Arthritis and/or other autoimmune diseases would be other than Type I Diabetes. Additionally, no one skilled in the art would presume that Type I Diabetes and the impaired glucose tolerance or Diabetes of the Metabolic Syndrome are the same condition or that they would be treated in the same way. Anyone trying to treat a person with the Metabolic Syndrome in the same way as one would treat a person with Type I Diabetes would be making a serious medical error. Anyone making such presumptions is certainly not someone who is skilled in the art.

The Examiner should be complemented, as, after reviewing the instant application, she has been able to predict the potential practice of medicine which derives from our discovery. It is not obvious without the information (data AND reasoning) revealed in our application. The fact that it is logical once our information is revealed actually defends the patent application. Hence, the claims should be granted.

I declare under penalty of perjury that the foregoing statements are true. Subscribed at New Orleans, LA, January 4, 2008.

Marise S. Gottlieb

Dr. Marise S. Gottlieb